**A multifactorial immunomodulatory protocol -promoting T-regulatory cells- prolongs graft and patient survival after intestinal transplantation**

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**Abstract** *(300 words, max 300 words)*

*Objective*

Translate to clinical Intestinal Transplantation (ITx) an Immunomodulatory Protocol (IP), experimentally-proven to activate T-regulatory (Tregs)-dependent graft protective mechanisms.

*Background*

ITx outcome (international registry 10y graft/patient survival: 41%/47%) remains inferior to other organs, due to frequent rejection, stronger immunosuppression (IS) and more IS-side-effects (fatal infections, malignancies, (nephro)-toxicity). The experimentally-proven IP consists in: periTx Donor-Specific-Blood Transfusion (DSBT) (promotes T-regs); avoiding high-dose steroids/calcineurin-inhibitors (CI) (abrogates DSBT-effect and inhibits T-regs); maneuvers to reduce reperfusion injury/endotoxin translocation (provokes rejection).

*Patients and Methods*

The IP was applied (2000-2014) to 13 consecutive ITx (5Isolated/8Liver-containing) from deceased donors. Collected data were: Demographics; Panel-Reactive-Antibodies (PRA); crossmatch, HLA mismatch; early(<3mo)/late(>3mo) Acute Rejection (AR); Chronic Rejection (CR); fatal infections and malignancies. At last follow-up we analyzed: Donor Specific Antibodies (DSA); circulating CD4+CD45RA-FoxP3hi memory T-regs {*versus* 11 IS-free Tolerant KidneyTx (Tol-KTx), 5 Healthy Volunteers (HV), 26 stable IS-KTx, 15 KTx with CR (CR-KTx)}; eGFR; TPN-independence; Quality-of-Life/(Karnofsky) and 10y graft/patient survival (Kaplan-Meier). Results are reported as mean(+/-SD).

*Results*

Age at ITx was 33y(+/-19y4mo); 5males/8females. PRA/crossmatch were negative. HLA-A/B/DR mismatches were: 1.2(+/-0.7)/1.7(+/-0.6)/1.3(+/-0.8). Early AR developed in 2(15%); late AR in 3(23%) (1 non-compliance); all were reversible. No CR occurred. One fatal aspergillosis following anti-rejection therapy occurred at 8.5mo. Another patient died to NSAID-induced graft enteropathy at 12y. No malignancies developed. At last follow-up {5y3mo(+/-4y6mo)} no DSA were detected; High memory T-regs frequency {1,82%(+/-0,08)} was found, comparable to Tol-KTx ($p=0.59$) and significantly higher than HV ($p<0.001$), stable IS-KTx ($p<0.01$), and CR-KTx ($p<0.001$); eGFR was 90ml/min(+/-42); All 11 survivors were TPN-free; Karnofsky-score in 8 recipients with follow-up >1y was >90%; 10y graft/patient survival was 90%.

*Conclusion*

Administration of DSBT in a protolerogenic environment {low steroids/CI; containment of inflammation and endotoxin-translocation} seems to permanently activate graft protective memory T-regs at levels unexpectedly similar to Tol-KTx recipients, without causing sensitization. This IP limits rejection without classically resorting to profound IS, thereby prolonging ITx survival.